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Transverse relaxation rates of pulmonary dissolved-phase Hyperpolarized ^{129}Xe as a biomarker of lung injury in idiopathic pulmonary fibrosis

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Abstract

Purpose: The MR properties (chemical shifts and R_2^* decay rates) of dissolved-phase hyperpolarized (HP) ^{129}Xe are confounded by the large magnetic field inhomogeneity present in the lung. This work improves measurements of these properties using a model-based image reconstruction to characterize the R_2^* decay rates of dissolved-phase HP ^{129}Xe in healthy subjects and patients with idiopathic pulmonary fibrosis (IPF).

Methods: Whole lung MRS and 3D radial MRI with four gradient echoes were performed after inhalation of HP ^{129}Xe in healthy subjects and patients with IPF. A model-based image reconstruction formulated as a regularized optimization problem was solved iteratively to measure regional signal intensity in the gas, barrier, and red blood cell (RBC) compartments, while simultaneously measuring their chemical shifts and R_2^* decay rates.

Results: The estimation of spectral properties reduced artifacts in images of HP ^{129}Xe in the gas, barrier, and RBC compartments and improved image SNR by over 20%. R_2^* decay rates of the RBC and barrier compartments were lower in patients with IPF compared to healthy subjects ($P < 0.001$ and $P = 0.005$, respectively) and correlated to DL_{CO} ($R = 0.71$ and 0.64 , respectively). Chemical shift of the RBC component measured with whole lung spectroscopy was significantly different between IPF and normal subjects ($P = 0.022$).

Conclusion: Estimates for R_2^* in both barrier and RBC dissolved-phase HP ^{129}Xe compartments using a regional signal model improved image quality for dissolved phase images and provided additional biomarkers of lung injury in IPF.

Keywords

hyperpolarized; xenon; idiopathic pulmonary fibrosis; model-based reconstruction; R_2^* ; lung; MRI

Introduction

Hyperpolarized xenon-129 (HP ^{129}Xe) MRI has emerged as a safe (1–3) and effective technique for investigating regional ventilation and gas exchange within the lungs (4). Due to its high solubility in biologic media (5), xenon dissolves rapidly into the pulmonary parenchymal tissues and bloodstream upon inhalation. Additionally, when dissolved in the pulmonary tissues, local chemical environments cause a 200 ppm chemical shift relative to ^{129}Xe in the airspaces of the lung (6–8). This “dissolved phase” of HP ^{129}Xe can be further separated into at least two spectral peaks: ^{129}Xe bound to hemoglobin in the red blood cells (RBC) at 218 PPM and ^{129}Xe in solution within the barrier (comprising the parenchymal tissues and blood plasma) at 198 PPM (7,9,10).

Over the past decade, advances in the hyperpolarization of ^{129}Xe , advanced pulse sequences using radial trajectories, and improved image reconstruction techniques have enabled volumetric imaging of the separated RBC and barrier components of dissolved-phase HP ^{129}Xe (11,12). Using these methods, biomarkers derived from images of RBC and barrier uptake have been shown to be sensitive to pulmonary pathology, including idiopathic pulmonary fibrosis (IPF) (13), pulmonary vascular disease (PVD) (14), chronic obstructive pulmonary disease (COPD) (15), and asthma (15).

Most measurements of the chemical shift frequencies and peak full-width at half-max (FWHM) (16) for the dissolved-phase components in human subjects have been derived from whole lung spectroscopy. In addition to the dissolved-phase uptake, the spectral properties of the dissolved-phase components have been shown to be significantly different in healthy and diseased populations. Kaushik, et al. showed significantly reduced FWHM of both the RBC and barrier peaks in IPF compared to healthy subjects, and significantly lower chemical shifts in the RBC compartment in IPF patients (16). Additionally, techniques for volumetric dissolved phase imaging (11,12) utilize whole lung spectroscopy to estimate the chemical shifts and transverse relaxation rates (R_2^* , using the relation $R_2^* \cong \pi \text{FWHM}$) of the dissolved-phase components, which are then used to constrain spectral separation for image reconstruction.

Pioneering work using a single-breath chemical shift imaging approach introduced the promise of chemical shift and R_2^* measurements in dissolved phase HP ^{129}Xe as a possible marker of interstitial lung disease (17–19). Because regional B_0 inhomogeneities will cause increased dephasing of the HP ^{129}Xe signal in both dissolved phase compartments, values estimated globally or within large voxels without measurement and estimation of the regional B_0 are expected to overestimate the R_2^* decay rate. Similarly, values derived from whole lung spectroscopy are also confounded by the large magnetic field inhomogeneities present in the lung. Errors in the estimation of these properties may lead to biases in the

reconstructed images, and can potentially reduce the utility of these properties as a marker of lung injury.

In this work, we present a novel, model-based reconstruction of HP ^{129}Xe in the airspaces, RBC, and barrier tissues and more fully investigate estimation of the chemical shifts and R_2^* values of each compartment as possible image biomarkers in patients with idiopathic pulmonary fibrosis (IPF). We hypothesize that by estimating these properties using a signal model that accounts for the spatially varying B_0 field, we can measure the chemical shifts and R_2^* values of the dissolved-phase components more accurately than whole lung spectroscopy, resulting in improved parameter estimates and image quality. Furthermore, we show that the proposed measurement of R_2^* in the dissolved-phase HP ^{129}Xe compartments that is derived using this method is a promising marker of lung injury in patients with IPF.

Theory

Signal Model

The acquired HP ^{129}Xe signal consists of magnetization in the airspaces, barrier tissues, and RBC compartments of the lung. Due to the different molecular environment, ^{129}Xe exhibits distinct resonant frequencies and relaxation rates in these regions. Regional magnetic field inhomogeneities ($\psi(\vec{x})$) cause additional, regionally varying frequency shifts in the measured signal. Lastly, due to the non-equilibrium hyperpolarization of the ^{129}Xe spins, longitudinal magnetization decays over the course of the scan due to T_1 relaxation and RF excitation.

Accounting for these signal dynamics, we derive the following signal model for each repetition (n) and acquisition sample timepoint (t) acquired:

$$s_{n,t} = w_n \sum_{c=g,b,r} FT_{\vec{k}}^{\rightarrow} \left[\rho_c(\vec{x}) e^{(2\pi i f_c - R_{2c}^*)t} e^{2\pi i \psi(\vec{x})t} \right], \quad \#(1)$$

Where $\vec{x}$ is the spatial position; $FT_{\vec{k}}^{\rightarrow}$ is the forward non-uniform fast Fourier transform (20) evaluated at the spatial frequency $\vec{k}$ as a function of n and t ; $\rho_c(\vec{x})$ are the spin densities of HP ^{129}Xe in their respective compartments (c), including gas (g), barrier (b), and RBC (r); f_c and R_{2c}^* are the frequency shift and relaxation rate of HP ^{129}Xe in each compartment; and w_n is a correction term accounting for the decrease in the magnitude of the longitudinal signal with each TR due to T_1 and RF-induced decay here normalized such that $w_1 = 1$.

Due to the large number of time points (degrees of freedom) acquired during a single TR and the spatial dependence of the B_0 field inhomogeneities, it would be computationally impractical to evaluate (Eq. 1) exactly as it requires a Fourier transform to be performed for each acquisition sample time t . The field inhomogeneity term is therefore approximated for finite time intervals as described in Sutton et. al. (21):

$$e^{2\pi i \psi(\vec{x})t} \cong \sum_{j=0}^l a(t, j) e^{2\pi i \psi(\vec{x})j\tau} \quad \#(2)$$

where l is the number of time points used, τ is the length of each time segment, and $a(t, j)$ are interpolation coefficients calculated to minimize the maximum error (21).

We apply this approximation to (1) using four time points and pull the spatially independent species frequency and R_2^* terms outside of the Fourier transform, yielding a signal model that requires only 12 (3 species by 4 time points) evaluations of the Fourier transform:

$$s_{n,t} = w_n \sum_{c=g,b,r} e^{(2\pi i f_c - R_{2c}^*)t} \sum_{j=0}^3 a(t, j) FT_{k,n,t} \left[\rho_c(\vec{x}) e^{2\pi i \psi(\vec{x})j\tau} \right]. \quad \#(3)$$

Model-based reconstruction

We define a regularized optimization problem to iteratively estimate the variables of the signal model from the acquired imaging data in k-space (y) as follows.

$$\rho_c(\vec{x}), \psi(\vec{x}), f_c, R_{2c}^*, w_n = \underset{t, n}{\operatorname{argmin}} \sum \left\| s_{n,t}(\rho_c(\vec{x}), \psi(\vec{x}), f_c, R_{2c}^*, w_n) - y_{n,t} \right\|_2^2 + R(\rho_c(\vec{x}), \psi(\vec{x})) \quad \#(4)$$

where R is the regularization operation, here the sum of the L_2 norms of the total variation operator, acting on the spin densities and magnetic field inhomogeneity map. This regularization was chosen to reduce noise in the spin density images and to enforce a smooth B_0 field map.

Optimization of this function was performed iteratively, alternating between minimizing with respect to the spatial variables ($\rho_c(\vec{x}), \psi(\vec{x})$) and the global model variables (f_c, R_{2c}^*, W). The spatial variables were estimated using the CG_DESCENT algorithm (22), while the remaining variables were estimated using a Trust-Region-Reflective optimization algorithm implemented in MATLAB (The MathWorks R2019b, Inc., Natick, Massachusetts). The Trust-Region-Reflective is a method of constraining non-linear optimization (23,24) that improves convergence for both large sparse problems and small dense problems. This algorithm is built into the optimization algorithms of Matlab R2019b. The estimation process is summarized in Figure 1.

Methods

Subject Recruitment

Eight healthy (H) subjects and 16 patients with IPF (diagnosed according to the ATS/ERS criteria (25)) underwent HP ^{129}Xe MRI on a 1.5T scanner (General Electric, Waukesha, WI) using a quadrature vest coil tuned to the xenon resonant frequency of 17.66 MHz (Clinical MR Solutions, Brookfield, WI). Informed consent was obtained in accordance with approved Institutional Review Board (UW IRB 2013–0266 and UW IRB 2014–1572) and investigational new drug (FDA IND# 118077) protocols. The study population also underwent pulmonary function tests, including measurements of DL_{CO} , forced vital capacity (FVC), and forced expiratory volume in one second (FEV_1). Summary statistics of the study population are summarized in Table 1.

Xenon Polarization and Delivery

^{129}Xe gas (85% isotopically enriched; Linde Gases, Stewartsville, NJ) was hyperpolarized via spin-exchange optical pumping (26) using a commercially available polarizer (Polarean Model 9820, Durham, NC). Either 200mL or 1L of gas, depending on the scan was collected into an ALTEF bag fitted with a quick-disconnect attachment and administered using a mouthpiece and a non-rebreather valve (See Supporting Information Table S1 and Supporting Information Figure S1). Subjects were coached to exhale to functional residual capacity (FRC), during which the bag was connecting to the mask, and then gas was inhaled followed by a breath hold of 15 seconds.

MR Spectroscopy

Whole lung spectroscopy and flip angle calibration was performed prior to imaging. Subjects inhaled a mix of 200 mL of HP ^{129}Xe and 800 mL of nitrogen for a 15 second breath hold during which 200 free induction decays (FIDs) were acquired (512 points, 32 μs sample rate, $\text{TR} = 20$ ms, $\text{TE} = 0.7$ ms, flip $\approx 15^\circ$). ^{129}Xe was excited using a Shinnar-Le Roux (SLR) RF pulse (1.2 ms, 5 kHz bandwidth) centered at the estimated RBC resonant frequency (17.6584 MHz) and designed to have minimal stop band ripple (0.1%) to minimize excitation of the gas-phase component. Despite careful pulse design, there was measureable excitation of the gas-phase with an estimated flip angle of 0.05 to 0.3 degrees. The acquired FIDs were averaged together and fit to Lorentzian peaks in the time domain, as in Robertson et al. (27). Flip angle calibration was performed from 150 FIDs acquired at the gas resonance in the same scan (following the dissolved-phase excitations described above). The center of k-space from these data was fit to an exponential from which the flip angle could be estimated.

MRI Acquisition

After whole lung spectroscopy followed by a 3–10 min period of resting tidal breathing, subjects were administered a 1L dose of pure HP ^{129}Xe and performed an additional 15-second breathhold during which spectroscopic images were acquired. As in the sequences of Qing and Kaushik (11,12), we employed an interleaved 3D radial acquisition of the dissolved-phase and gas-phase signals. Frequency spacing for dissolved and gas-phase

excitations was 3832 Hz. We acquired four gradient echoes of both the dissolved-phase and gas-phase signal in each TR, as depicted in Figure 2. The imaging scan utilized the same 1.2 ms SLR RF pulse as the whole lung spectroscopy/calibration scan described above, with the transmit power calibrated to the desired flip angles. Scan parameters are TEs/TR: 0.9, 2.0, 3.1, and 4.2 ms / 15 ms, FOV: 400 mm, resolution: 6.25 mm isotropic, 1008 projection angles, 492 points per projection angle, BW: 62.5 kHz, dissolved flip angle: 22°, gas flip angle: 0.5°.

Image Reconstruction

Images were reconstructed using the proposed novel regularized, signal model-based reconstruction described in the Theory section, implemented in MATLAB. The reconstruction workflow is summarized in Figure 1. First, an estimate of the gas spin density image and B_0 field map were reconstructed using the on-resonance gas-phase data by reducing the signal model (Eq. 3) to a single spectral component. The resulting estimate of $\psi(\vec{x})$ was then used to initialize the dissolved-phase reconstruction problem and iteratively solve the optimization problem (Eq. 4) as described in the Theory Section. Estimates of the frequencies and R_2^* rates of the components derived from whole lung spectroscopy were also used to initialize the reconstruction. The correction factor for the decay of longitudinal magnetization with each TR (w_n) was initialized from the first acquisition sample point at the center of k-space of each TR acquired. Convergence was reached after 8 repetitions of the reconstruction algorithm, resulting in 200 iterations of the CG_DESCENT optimization (22) of the spin densities and B_0 field inhomogeneity.

To evaluate the benefits of estimating the chemical shifts and R_2^* decay rates for each species during image reconstruction, images were also reconstructed while holding those properties fixed at the values measured from whole lung spectroscopy. This reconstruction, denoted hereafter as “No Estimation”, utilized the same regularization and same number of iterations as the full reconstruction described above.

Image post-processing

Regional maps of the ratios of dissolved-phase to Gas (Barrier:Gas and RBC:Gas) were calculated by dividing the reconstructed dissolved-phase images by the on-resonance gas image and correcting for the difference in flip angle, as in Kaushik et. al. (12). RBC:Barrier ratio maps were determined similarly, with no flip angle correction needed. Lung masks were derived by thresholding the on-resonance gas image and manually removing the large airways. Mean values of the ratio maps over the lung volume were derived using these masks. Additionally, image SNR was calculated using the ratio of the average intensity within the lung mask to the standard deviation of the background noise.

Statistical Analysis

The statistical significance of differences in the mean ratios and spectral properties (frequency and R_2^*) between healthy subjects and patients with IPF was assessed using the Wilcoxon Rank-Sum test. Differences between chemical shifts and R_2^* decay rates measured during whole lung spectroscopy and through image reconstruction were assessed

using the Wilcoxon signed rank test. The significance of correlations between these metrics and DL_{CO} %P was evaluated using the Spearman correlation metric. A p value <0.05 was considered statistically significant.

Results

Image quality improvements

Typical image results from the dissolved-phase and off resonance gas excitation are shown for two normal subjects of age 30 and 65 years in Figure 3. Note that the gas images shown in Figure 3 result from the off-resonance excitation of the gas component during the dissolved phase acquisition and not the interleaved gas acquisition optimized specifically for imaging of ventilation and the calculation of ratio maps. Images were reconstructed both with and without estimation of the chemical shifts and relaxation rates. When reconstructing using only the estimates of the frequencies and R_2^* derived from whole lung spectroscopy, significant image artifacts (arrows in Fig. 3) were observed in all three spectral species, yielding intense signal outside of the lung. These artifacts resolved after including estimation of the spectral properties in the reconstruction process. Estimation of the spectral properties also resulted in an improvement in dissolved-phase image SNR of over 20% across the study population, with RBC and barrier SNR increasing overall from 8.7 to 11 and 19 to 23, respectively. This is primarily driven by reduced image noise, likely due to reduced residual variance from a more accurate estimation of the model when including the R_2^* decay and spectral properties.

Dissolved-phase ratios

Dissolved-phase ratio maps for a healthy, 65 year old female subject are shown in Figure 4 derived from reconstructions both with and without estimation of the spectral properties. The two reconstructions yield similar regional distributions between them, with slightly lower RBC:Gas and RBC:Barrier measurements.

Patients with IPF exhibited significantly lower ratios of RBC:Gas (0.22% vs 0.30%, $p=0.022$, Figure 5A) and RBC:Barrier (20.2% vs 32.8%, $p<0.001$, Figure 5C) compared to healthy subjects, agreeing with previous results (13). Contrasting with previous results, mean Barrier:Gas was not significantly different (1.11% vs 0.93%, $p=0.23$, Figure 5B) between the populations likely due to the high degree of variability for Barrier:Gas in the IPF population in our study. Significant statistical correlations were observed between RBC:Gas and DL_{CO} % predicted ($R=0.43$, $p=0.034$, Figure 5D) and RBC:Barrier and DL_{CO} % predicted ($R=0.61$, $p=0.0014$, Figure 5F) but not for Barrier:Gas (Fig. 5E). The RBC:Barrier ratio showed the most significant difference between the populations and the strongest correlation ($r = 0.61$) with DL_{CO}% predicted. Additionally, mean ratios were compared between the full reconstruction and that with no estimation of the spectral properties using Bland-Altman analysis. We found minimal bias between ratios derived from the full and the “no estimation” reconstructions (RBC:Gas = -0.01% ; Barrier:Gas = 0.02% ; RBC:Barrier = -1.0%) with narrow 95% confidence intervals on the differences between the techniques (RBC:Gas = -0.08% to 0.05% ; Barrier:Gas = -0.21% to 0.25% ; RBC:Barrier =

–5.7% to 3.8%). Plots of the Bland-Altman analysis may be found in Supporting Information Figure S2.

Spectral property estimation

The frequency of gas-phase Xenon was set to 0 ppm, by definition. Estimates of the gas-phase Xenon frequency was not significantly different between whole lung spectroscopy and imaging data (0.1 ppm difference). Estimation of the chemical shifts (Figure 6) and R_2^* (Figure 7) properties during image reconstruction resulted in significantly different values than those estimated from whole lung spectroscopy across the study population. RBC chemical shifts were higher when measured from imaging data (217.4 ± 0.6 ppm) compared to spectroscopy (215.7 ± 0.9 ppm). Small increases were also observed for the barrier chemical shift (197.8 ± 0.2 ppm) compared to spectroscopy (197.5 ± 0.3 ppm). Both increases were significant ($p < 0.001$) under the Wilcoxon Signed Rank test. In whole lung spectroscopy, significant ($p = 0.022$) differences were observed in the RBC chemical shift between healthy subjects and IPF patients, in line with the observations of Norquay et al. (28), but no significant difference in the chemical shift of either species was observed when estimated during the image reconstruction process (Figure 6).

R_2^* decay rates of all species were observed to be significantly lower when estimated during the image reconstruction compared to whole lung spectroscopy. In patients with IPF, R_2^* was significantly decreased in both the RBC (363 s^{-1} vs. 477 s^{-1} , $p < 0.001$) and barrier (368 s^{-1} vs. 405 s^{-1} , $p = 0.005$) compartments compared to healthy subjects (Figure 7). While similar decreases were observed in whole lung spectroscopy, image-based estimates yielded a larger and more significant difference between the two populations, particularly in the RBC compartment. Mean values of the spectral properties observed in both healthy subjects and IPF patients are summarized in Table 2.

The estimated R_2^* values of both the RBC and barrier compartments were significantly correlated with $DL_{CO} \%$ predicted (Figure 8) both when estimated during image reconstruction and from whole lung spectroscopy. However, R_2^* values estimated from imaging data resulted in stronger correlations in both dissolved-phase compartments (Figure 8).

Discussion

By using a multi-echo acquisition and a model-based reconstruction, the spectral properties of the dissolved-phase signals in the barrier and RBC can be estimated directly during image reconstruction. Unlike in whole lung spectroscopy, values derived during image reconstruction are obtained while accounting for the large regional B_0 inhomogeneities of the lung, possibly yielding more accurate measurements as indicated by a reduction in image artifacts. While previous work in whole lung spectroscopy (16,27,29) has shown differences between healthy and diseased populations with respect to dissolved-phase peak FWHM (proportional to R_2^*), these differences become more significant when measured as part of the proposed model-based image reconstruction.

Differences in spectral properties between spectroscopy- and reconstruction-based measures

Values of HP ^{129}Xe R_2^* measured with the proposed model-based image reconstruction were significantly lower for both the barrier and RBC compartments compared to whole lung spectroscopy. This was expected, as the spectral peaks acquired during whole lung spectroscopy experience additional broadening due to the large B_0 inhomogeneity across the lung.

We also observed substantial differences in the measured dissolved-phase chemical shift between the two techniques. While the barrier chemical shift was slightly higher (0.2 ppm) when measured with the proposed model-based image reconstruction compared to whole lung spectroscopy, large increases were observed in the RBC chemical shift: 0.8 ppm (14 Hz at 1.5 T) in healthy subjects and 2.2 ppm (30 Hz) in IPF patients. We attribute these changes primarily to the difference in acquisition times between the two techniques; FIDs are acquired during whole lung spectroscopy for 16 ms (512 points $\times$ 32 μs), while during imaging each projection is only acquired for 5 ms. The shorter acquisition time of the imaging sequence yields a reduced impact of susceptibility induced magnetic field gradients, both on the macroscopic scale in terms of the B_0 inhomogeneities across the lungs and on the microscopic scale at the alveolar surface. Robertson et. al. (27) demonstrated that microscopic susceptibility effects on HP ^{129}Xe in the alveolar surface modeled using a two-Lorentzian model for the barrier compartment resulted in significantly increased estimations of the RBC chemical shift. Similarly, our group recently showed (30) that using a susceptibility based signal model (31) for HP ^{129}Xe in the barrier compartment in whole lung spectroscopy yielded similar increases in the RBC chemical shift compared to conventional processing techniques. These effects are more prominent at later acquisition times, due to the increased phase accrual of the susceptibility induced off-resonance, resulting in the observed differences in measured chemical shifts between the shorter acquisition of imaging and the longer acquisition of spectroscopy.

To support this hypothesis, the spectroscopy data was reprocessed using only the first 5 ms of the acquired FIDs. This resulted in increased relative RBC (1.2 ppm) and Barrier (0.3 ppm) chemical shifts compared to the results using the full 16 ms data acquisition time. These results are shown in Supporting Information Figure S3.

R_2^* as a marker of lung injury

HP ^{129}Xe rapidly exchanges between the airspaces, barrier tissues, and RBC in the lung. This exchange between compartments with different chemical shifts is an additional source of dephasing, as described by the McConnell-Bloch equations of the NMR signal due to chemical exchange (32). Solutions to these equations show that increased rates of exchange between compartments will result in more rapid signal decay, as measured through the effective R_2^* . We hypothesize that the decreased R_2^* values measured in the RBC and barrier compartments in patients with IPF is due to reduced rates of exchange of HP ^{129}Xe between the airspaces, tissues, and blood. This is supported by the strong positive correlation with DL_{CO} , suggesting that reduced R_2^* is correlated with reduced diffusion of gas into the

bloodstream as would be expected if, for example, the barrier thickness were to increase or local perfusion were to decrease.

Measurements of RBC:Gas, Barrier:Gas, and RBC:Barrier have been shown to depend on the total amount of HP ^{129}Xe transferred during an effective exchange time (33). This amount transferred will depend on the exchange rates of Xenon into these compartments, the sequence parameters chosen (33), density of the barrier tissues present, and perfusion of the lung. Assuming equivalent sequence parameters are used, changes in both rates of exchange and volume of tissue may explain our measures of R_2^* in the IPF population: these subjects may be exhibiting a combination of increased barrier tissue density due to inflammation or fibrosis, and a loss of perfusion due to vascular remodeling (34). We hypothesize that measurements of R_2^* in the barrier and RBC compartments are more directly related to regional rates of HP ^{129}Xe exchange than ratio measures, and thus may provide a more sensitive biomarker of lung injury.

Reconstruction of off-resonant gaseous HP ^{129}Xe

Existing volumetric imaging techniques require that there be no RF excitation of the off-resonant gaseous HP ^{129}Xe signal during acquisition of the dissolved-phase (11,12). This has proven to be a significant challenge due to broadband RF hardware performance, limiting flexibility in the flip angles used (35) and in some cases requiring careful, hardware-specific calibration of the RF pulse (12). The ability to isolate contaminating off-resonance gas signal through model-based reconstruction can relax constraints on RF-pulse design to allow for reduced TE and improved SNR for dissolved phase components. While prior work has demonstrated reconstruction of HP ^{129}Xe in the RBC, barrier, and off-resonant gas compartments from a single excitation for only 2D projection images (36), this work represents the first volumetric reconstruction all three phases from a single excitation. This allows for imaging in the presence of off-resonance gas excitation during dissolved-phase acquisition, allowing for more flexibility in RF pulse design than previous spectral separation techniques.

Study limitations and future work

At present the R_2^* estimates derived from the signal model-based image reconstruction are assumed to be constant across the lung volume. This assumption was necessary in the current work to enforce robust convergence. However, lung injury in IPF (and generally in pulmonary diseases) is expected to vary regionally within the lung. Further work is needed to develop the reconstruction methodology to be sufficiently robust to estimate R_2^* regionally. We have also assumed sufficiently rapid mixing of the gas and dissolved phase compartments such that they share a common approximately monoexponential T1 and RF signal decay to simplify estimation of the weighting factor, w_n . Additionally, the proposed model-based reconstruction is more computationally expensive than previously reported techniques used to separate the RBC and barrier compartments (11,12), with average 3D image reconstruction times of approximately one hour on a single core of an Intel Xeon processor (Intel Corp., Santa Clara, CA). However, we expect that optimization of the reconstruction code, including porting to C++ and taking advantage of parallel computing capabilities, will significantly decrease the processing time required. Finally, doses of gas

were delivered at a fixed 1L volume, which results in variable relative lung inflations across the cohort. This will result in some additional variations in the ratios computed, independent of disease.

Conclusion

We have developed a regularized, model-based reconstruction of pulmonary dissolved-phase HP ^{129}Xe MRI that estimates R_2^* for barrier and RBC compartments as a potential biomarker of lung injury. By estimating independent chemical shifts and R_2^* values of HP ^{129}Xe in the airspaces, barrier, and RBC during image reconstruction, this method yields reduced image artifacts and thus improved image quality. Dissolved-phase R_2^* measurements derived from the image reconstruction correlate strongly with disease status and lung function when comparing IPF to healthy subjects, providing a novel, sensitive biomarker of lung injury using HP ^{129}Xe MRI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
 Optimization procedure for estimating dissolved-phase HP ^{129}Xe images and spectral properties.

Figure 2:

Diagram of the pulse sequence used for image acquisition in this study. Transmit and receive frequencies were alternated between the RBC resonance and the gas resonance for each half of the TR acquired. Note that RF amplitudes are not to scale.

Figure 3:

Images of off-resonance Gas, Barrier, and RBC in two healthy subjects reconstructed without (left) and with estimation (right) of the spectral properties. Note that the gas images shown here are from the off resonance gas excited during acquisition of the dissolved-phase and not the interleaved gas acquisition optimized specifically for imaging of ventilation and the calculation of ratio maps. Reconstruction without estimation of HP ^{129}Xe spectral properties results in image artifacts indicated by arrows (seen most prominently in the older subject), while reconstruction with estimation of the spectral properties of each compartment resolves the observed image artifacts and improves overall SNR.

Figure 4: Dissolved-phase ratio maps of a healthy subject (65 year old female) calculated without (left) and with (right) estimation of the spectral properties. Histograms of the ratios over the lung volume are shown to the left. Notably, both RBC:Gas and RBC:Barrier showed slightly lower values when determined with the full reconstruction compared to that with no estimation of spectral properties in this subject.

Figure 5:

Mean ratios of (A) RBC:Gas, (B) Barrier:Gas, and (C) RBC:Barrier derived from MR spectroscopic model-based image reconstruction in healthy subjects (H) and patients with idiopathic pulmonary fibrosis (IPF). Patients with IPF had significantly lower RBC:Gas ($p < 0.05$) and RBC:Barrier ($p < 0.001$) ratios. These ratios were compared to DL_{CO} % predicted in the study subjects (D-F). Significant correlations were observed between DL_{CO} and RBC:Gas (A), and DL_{CO} and RBC:Barrier (C), but no correlation was observed between DL_{CO} and Barrier:Gas (B).

Figure 6: Estimated chemical shifts of the RBC and barrier components estimated from MR spectroscopic model-based image reconstruction presented in this paper (left column) and from whole-lung MR spectroscopy (right column).

Figure 7:

Transverse decay rates (R_2^*) of HP ^{129}Xe in the RBC and Barrier compartments estimated from MR spectroscopic model-based image reconstruction described here (left column) and from whole lung MR spectroscopy (right column). Differences between populations are noted at a significance of $p < 0.05$ (*), $p < 0.01$ (**) and $p < 0.001$ (***).

Figure 8:

R_2^* estimated from MR spectroscopic model-based image reconstruction (left column) and whole lung MR spectroscopy (right column) vs. DL_{CO} % predicted in both healthy (H) subjects and patients with IPF. Spearman correlation coefficients (r) and associated p -values are shown. R_2^* values estimated during image reconstruction resulted in increased correlation with DL_{CO} .

Table 1:

Study population summary statistics. Mean values, standard deviations, and range of values are shown.

Subject Status	Healthy	Idiopathic pulmonary fibrosis	p-value
<i>N</i>	8	16	
<i>Sex</i>	4M, 4F	15M, 1F	
<i>Age (years)</i>	60±8 [45–69]	69±7 [56–85]	0.0099
<i>DL_{CO} % Predicted</i>	87±15 [69–105]	56±16 [30–84]	< 1e-3
<i>FVC % Predicted</i>	95±10 [83–113]	81±18 [51–110]	0.066
<i>FEV1 % Predicted</i>	96±10 [83–109]	86±19 [60–116]	0.23
<i>FEV1/FVC (%)</i>	78±6 [68–86]	80±6 [65–88]	0.68

Table 2:

Spectral properties of HP ^{129}Xe estimated via the image reconstruction process and whole lung spectroscopy in healthy (H) subjects and patients with IPF. Mean and standard deviations of the properties across each population are shown.

	RBC		Barrier		Gas	
<i>MR Imaging</i>	H	IPF	H	IPF	H	IPF
<i>Chemical shift (ppm)</i>	217.1±0.8	217.5±0.4	197.8±0.3	197.7±0.2		
<i>R₂[*] (1/s)</i>	477±34	363±49	405±19	368±28	18.5±2.5	17.3±4.6
<i>T₂[*] (ms)</i>	2.10±0.15	2.80±0.41	2.47±0.11	2.74±0.22	55±8	61±16
<i>MR Spectroscopy</i>	H	IPF	H	IPF	H	IPF
<i>Chemical shift (ppm)</i>	216.3±0.8	215.3±0.7	197.6±0.4	197.4±0.3		
<i>R₂[*] (1/s)</i>	573±22	545±22	464±16	436±16	64±16	71±10
<i>T₂[*] (ms)</i>	1.75±0.07	1.84±0.07	2.16±0.07	2.29±0.08	16.4±3.6	14.2±2.0